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Review

Orienting and Reorienting: The Locus Coeruleus Mediates Cognition through Arousal

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Mood, motivation, attention, and arousal are behavioral states having a profound impact on cognition. Behavioral states are mediated though the peripheral nervous system and neuromodulatory systems in the brainstem. The noradrenergic nucleus locus coeruleus is activated in parallel with the autonomic system in response to biological imperatives. These responses can be spontaneous, to unexpected salient or threatening stimuli, or they can be conditioned responses to awaited behaviorally relevant stimuli. Noradrenaline, released in forebrain structures, will facilitate sensory processing, enhance cognitive flexibility and executive function in the frontal cortex, and promote offline memory consolidation in limbic structures. Central activation of neuromodulatory neurons and peripheral arousal, together, prepare the organism for a reorientation or reset of cortical networks and an adaptive behavioral response.

Introduction

Behavioral state is defined by psychological variables including mood, motivation, stress, arousal, vigilance, and attention and is determined by environmental factors such as salient or threatening stimuli including reward and punishment, and homeostatic challenges like extreme heat or cold, light or dark, and hunger or thirst. Behavioral state is mediated in the body by responses of the peripheral nervous system to environmental challenges, resulting in release of hormones into the bloodstream. In the brain, activity of neuromodulatory neurons, grouped within nuclei of the midbrain and brainstem, covaries with these psychological and physiological factors, thereby mediating behavioral state in the central nervous system. This is how cognitive processes, including focused attention, learning, memory, and even perception are impacted by the behavioral state. We know this from our own subjective experience as well as from reports of educators and clinicians. Carefully controlled experimentation, in which cognitive performance and physiological correlates of behavioral state are monitored together, has contributed solid evidence that cognition is greatly influenced by behavioral state and activity of neuromodulatory systems that covary with these states.

Brainstem neuromodulatory systems having a significant impact on arousal, vigilance, mood, and cognition include the serotonergic dorsal Raphé nucleus (DR), the noradrenergic nucleus locus coeruleus (LC), the midbrain dopaminergic neurons of the ventral tegmental area (VTA), and the substantia nigra pars compacta (SNc). The histofluorescence method developed in the early 1960s allowed the visualization of these nuclei and their projection pathways in the rat brain and revealed a remarkably similar organization in that the cell bodies are found in rather compact nuclei with widespread axonal projections to distant forebrain regions (Dahlstrom and Fuxe, 1964). Cholinergic nuclei in the brainstem (lateral dorsal tegmental nucleus and pedunculopontine nucleus [LDT/PPN]) and basal forebrain area (nucleus basalis of Meynert [NBM]) have similar anatomical organization and are also implicated in the regulation of vigilance and cognitive function (Jones, 2008). In addition to their distal forebrain projections, the neuromodulatory nuclei have multiple reciprocal connections. The LC has strong projections to all of the others and receives direct input from its neighbor LDT/PPN and from DR. The DR also projects to VTA and NBM, thereby influencing both dopamine (DA) and cholinergic input to the cortex (Hervé et al., 1987). To add to the complexity of the situation, these systems interact at the level of axon terminals by reciprocal modulation of release of transmitters. For example, noradrenaline (NA), acting at alpha 2 adrenoceptors located on terminals of all four neuronal types, inhibits release of their transmitters. At the same time, there are mutual increases of release of DA and NA via alpha 1 and D1 receptors, respectively, in the prefrontal cortex (PFC) (Pan et al., 2004) and acetylcholine provokes a calcium-dependent release of both DA and NA via a muscarinic receptor (Rao et al., 2003).

Ultimately, an understanding of the concerted action of neuromodulatory systems will reveal how behavioral states influence, promote, or even permit cognitive activity (Briand et al., 2007). Nevertheless, in our view, a great deal has yet to be understood about the relative contribution of each one of these systems in attention, perception, reward and punishment, learning, and memory. Here, we address the specific role of the noradrenergic nucleus locus coeruleus in modulating forebrain networks mediating cognitive activity.

In addition to strongly innervating all of the other neuromodulatory nuclei, the LC sends projections to all cortical regions, as well as to thalamic nuclei, septum, hippocampus, and basal lateral amygdala (Loughlin et al., 1986; Figure 1). Moreover, LC is the sole source of noradrenergic innervation to these

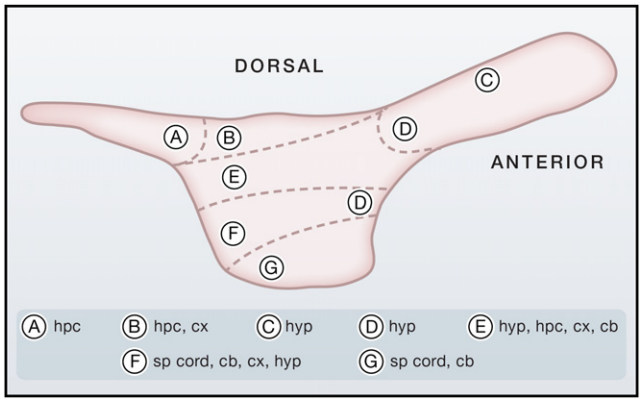

Figure 1. The Locus Coeruleus
Sagittal schematic view of the rat locus coeruleus. The subdivisions indicated on the figure and the legend are those proposed by Loughlin et al. (1986), from whom the figure has been adapted. Subdivisions reflect an intrinsic organization with respect to efferent projections of LC. Abbreviations: hpc, hippocampus; cx, cortex; hyp, hypothalamus; cb, cerebellum; sp cord, spinal cord.

structures (Jones and Moore, 1977; Moore and Bloom, 1979; Asan, 1998; Samuels and Szabadi, 2008; Figure 1). Multiple approaches using lesions, pharmacology, and transgenic technology combined with behavioral analysis and in vitro and in vivo electrophysiological recording in target regions have generated a large literature and contributed much to our knowledge of how NA acts in the brain. Noradrenergic action in thalamus and cortex strongly influences arousal and behavioral state (Berridge et al., 1993; Berridge and Waterhouse, 2003). In addition, acting through thalamic nuclei and sensory cortices, locus coeruleus activity provides gating and tuning influences on sensory processing in all modalities (e.g., McLean and Waterhouse, 1994; Waterhouse et al., 1998; Bouret and Sara, 2002; Lecas, 2004; Devilbiss and Waterhouse, 2011). Projections to hippocampus regulate synaptic plasticity in this region, as demonstrated by early work from the laboratories of C. Harley and J. Sarvey (Neuman and Harley, 1983; Stanton and Sarvey, 1985; Dahl and Sarvey, 1989; Harley, 2007). Together with hippocampal action, LC projections to the amygdala play an important role in memory consolidation, particularly by interacting with opioids and other neuropeptides (Gallagher et al., 1985; McIntyre et al., 2012). In frontal cortex, noradrenaline has been shown to be essential for working memory and focusing of attention (Ramos and Arnsten, 2007 for review; Arnsten et al., 2012, this issue of *Neuron*). Finally, there is a growing body of evidence from rodent, primate, and human studies that the noradrenergic system plays an important role in attentional shifting and behavioral flexibility (Devauges and Sara, 1990; Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Yu and Dayan, 2005; McGaughy et al., 2008). All of this extensive work, spanning four decades, underscores the importance of noradrenaline in promoting or even permitting basic cognitive processes. To a large extent, we know which noradrenergic receptors are implicated within particular brain regions, as well as which intracellular signaling cascades are involved. What is lacking is a clear definition of the factors, external and internal, governing the activity of LC neurons. Since the small number of neurons of the LC (~1,500 in rodents, ~15,000 in primates) is the sole source of noradrenaline in most forebrain regions, this is an essential step in understanding how the system modulates cognition. The rest of this Review will focus on the environmental and cognitive contexts governing the activity of LC neurons. We will see the extent to which LC activity relates to autonomic arousal and how it can promote cognitive functions, especially those that depend upon the prefrontal cortex, in a way that is strikingly in line with the idea of truncated conditioned reflex proposed by Kupalov many years ago (Kupalov, 1935, 1961; cited in Giurgea, 1974, 1989).

Afferent Input to Locus Coeruleus

Anatomical inputs to LC have been a historically controversial issue (Cedarbaum and Aghajanian, 1978; Ennis and Aston-Jones, 1986) that is being resolved by improvement of anatomical track-tracing methods along with immunofluorescence and immunoelectron microscopic techniques to permit ultastructural analysis (Luppi et al., 1995; Tjoumakaris et al., 2003; Pfaff et al., 2012). In addition to major inputs from the brainstem nucleus gigantis cellularis (NGC) and its neighboring paragigantis cellularis (PGi) and the prepositus hypoglossal nucleus, LC afferents include the paraventricular nucleus of the hypothalamus (PVN), Barrington's nucleus, central nucleus of the amygdala, and inputs from the other major neuromodulatory nuclei, as discussed above. The vagus nerve transmits information from the autonomic nervous system to LC via the nucleus tractus solitarii (NTS), which has a direct projection to the dendritic region of the LC (Van Bockstaele et al., 1993). Rapid input from the periphery is also transmitted from the PVN of the hypothalamus, which also sends axons directly to the noradrenergic dendrites of the LC (Reyes et al., 2005). The only direct cortical input comes from prefrontal areas in primates and rodents (Arnsten and Goldman-Rakic, 1984; Luppi et al., 1995). Although the input is relatively sparse with only about 6% of cells from the frontal region in the rat driven antidromically by LC stimulation (Sara and Hervé-Minvielle, 1995), it exerts a potent effect on LC neurons (Sara and Hervé-Minvielle, 1995; Jodo et al., 1998).

LC Arousal and Vigilance

It was first reported more than 50 years ago that the activity of LC neurons fluctuates with the sleep-wake cycle and levels of cortical vigilance, presumably via subcortical inputs (Roussel et al., 1967; Hobson et al., 1975; Aston-Jones and Bloom, 1981a; Berridge et al., 1993). Because increase in LC activity tends to anticipate transition from sleep to wakefulness, the prevailing view has been that LC plays a causal role in the induction and regulation of cortical arousal (Berridge, 2008 for comprehensive review). Recent studies using optogenetic techniques to manipulate LC activity confirms its essential role in the sleep-wakefulness cycle and in behavioral and cortical arousal (Carter et al., 2010). Nevertheless, cortical influence on LC activity, documented in the previous section, should modulate LC responses in a context-dependent manner. For instance, LC response to a distractor, an unexpected event, may be attenuated when the subject is focused on the task at hand, but the LC response to an awaited, task-relevant cue is enhanced.

LC and Stress

In addition to the relatively slow tonic changes in firing rate in relation to arousal states, the LC is reliably and robustly activated by acute stressors, both visceral and environmental, as indicated by a very large literature spanning 40 years (Korf et al., 1973; Valentino and Van Bockstaele, 2008). Electrophysiological recording of LC unit activity shows that LC cells respond biphasically or multiphasically to noxious footshock stimulation, probably through the PGi, from neurons in the dorsal horn (Palkovits et al., 1999). The response is typically a short-latency burst followed by a brief inhibition, a subsequent increase in firing rate lasting up to 200 ms, followed by a long period of inhibition. All LC cells show this pattern of response, with little habituation, even after many repetitions of the stimulation (Hirata and Aston-Jones, 1994; Chen and Sara, 2007). LC neurons are activated by visceral stressors including bladder distention, changes in blood volume, and heat and cold (Jacobs et al., 1991; Valentino and Van Bockstaele, 2008). LC activation by stressors closely parallels a number of autonomic responses in the periphery (Abercrombie and Jacobs, 1987; Svensson, 1987), presumably mediated by input from the vagus nerve via a direct projection to LC from the NTS (Van Bockstaele and Aston-Jones, 1995). Another structure potentially mediating the effect of stress is the central nucleus of the amygdala, which is also involved in triggering autonomic reactions to conditioned stressors (LeDoux et al., 1988; Reyes et al., 2011). The influence of the central nucleus of the amygdala on LC is mediated, in part, through release of corticotrophin releasing factor (CRF) (see Valentino and Van Bockstaele, 2008 for detailed review). Electrical stimulation of the central nucleus of the amygdala elicits an excitatory response in LC that is blocked by a CRF antagonist (Bouret et al., 2003). Furthermore, lesions to the amygdala block stress-associated increase in monoamine release in the prefrontal cortex (Goldstein et al., 1996). A recent fMRI study in humans has shown a sustained increase in functional connectivity between the amygdala and the LC after a period of psychological stress (van Marle et al., 2010). This may serve to promote offline memory consolidation that is dependent upon the noradrenergic input to the forebrain for at least 2 hr after learning (Roullet and Sara, 1998; Tronel et al., 2004) and could account for the fact that highly emotional memories are enduring and compelling (McGaugh and Roozendaal, 2009). Chronic, repeated stress over several days leads to long-lasting hyperactivity and increased sensitivity of locus coeruleus neurons (Mana and Grace, 1997). It has been suggested that excessive activity in monoaminergic neurons during stress, and as an aftermath, is responsible for stress-induced deficits in cognitive function dependent upon the prefrontal cortex (Brennan and Arnsten, 2008; Arnsten, 2009).

Altogether, these data point to an exquisite sensitivity of LC neurons to arousing and stressful stimuli at both a short and extended time scale. The LC is under direct control of primary structures responding to stress from the periphery via the vagus nerve and from the PVN of the hypothalamus. Noradrenaline released by LC neurons would then mediate, or at least modulate, the stress or arousal response in forebrain regions. In a recent series of experiments in anesthetized rats, we recorded single unit activity simultaneously from prefrontal cortex, VTA, and LC in response to an electric shock stimulation to the hindpaw and observed robust, short-latency responses of LC neurons to a single stimulation. In contrast, responses in VTA and PFC neurons were only elicited by short trains of shock, never by a single pulse. Moreover, the response latencies from PFC and VTA were in excess of 100 ms, while responses of LC neurons were always under 30 ms. Critically, during inhibition of spontaneous activity of LC neurons by clonidine, there was no longer any response to footshock in the VTA or PFC (Pietrajtis et al., 2010, FENS, abstract). These results strongly suggest that the LC drives the responses in the upstream structures, the relatively short-latency response in LC most likely being elicited by input from the dorsal horn of the spinal cord (Cedarbaum and Aghajanian, 1978).

LC Response to Sensory Stimulation

Stimuli of all sensory modalities that are novel, but not necessarily stressful, elicit short-latency bursts of a few action potentials in the LC (Foote et al., 1980; Aston-Jones and Bloom, 1981b; Rasmussen et al., 1986; Sara et al., 1994). If a novel stimulus is not associated with a significant event such as a reward or punishment, the LC response habituates, the speed of the habituation being a function of the salience of the stimulus. This has been clearly demonstrated for the auditory modality with rapid habituation of responses to tones in anesthetized and awake rats (Hervé-Minvielle and Sara, 1995). In freely moving rats exploring a hole board, LC units increase tonic firing rate when the rat is transferred from the home cage to the novel hole board arena. After several sessions of familiarization, LC units do not show this increase associated with hole board exploration. If, however, novel objects are placed in the holes, LC units fire in a phasic burst, time locked with the encounter with the object (Vankov et al., 1995). The response to novelty rapidly habituates and disappears after the second or third inspection of the object. This hole board procedure has been used to behaviorally drive LC to demonstrate the role of beta adrenergic receptors in enhancing long-term plasticity in the hippocampus (Straube et al., 2003; Uzakov et al., 2005).

Conditioned Responses in LC

If the stimulus is followed by a significant event, a reinforcement, the LC response persists and is even enhanced. Conditioned responding in LC has been demonstrated in monkey (Aston-Jones et al., 1994; Bouret and Richmond, 2009), cat (Jacobs et al., 1991), and rat (Sara and Segal, 1991; Bouret and Sara, 2004). The acquisition of a conditioned response of LC neurons occurs in appetitively motivated as well as aversively motivated tasks (Sara and Segal, 1991). During the course of learning, LC responses to the stimulus associated with the reinforcement appear extremely rapidly, emerging after only a few presentations of the stimulus-reinforcement pairings, many tens of trials before behavioral expression of differential learning (Sara and Segal, 1991; Aston-Jones et al., 1997; Bouret and Sara, 2004) and before the appearance of conditioned responses in the medial frontal cortex (Bouret and Sara, 2004). During overtraining, LC task-related responses were diminished, while behavioral performance remained high. When the stimulus-reward contingencies were reversed, or reward was withheld, LC neurons immediately re-engaged in the task, on the second

reversal or extinction trial, responding to both CS+ and CS− (Sara and Segal, 1991). We observed a similar phenomenon in an odor discrimination task during reversal learning or during an intradimensional shift in which the rat had to learn new odor pairs (Bouret and Sara, 2004).

In a recent series of experiments in monkeys, we examined the relation of LC activity as a function of Pavlovian and instrumental responses emitted in the same reward schedule task (Bouret and Richmond, 2009). The activation of LC neurons was systematically associated with Pavlovian appetitive responses (lipping), which occurred both at the time of cue onset and at the time of instrumental responses (bar release). Thus, even if LC activation coincides with the initiation of a goal-directed action, it seems to be related to an underlying Pavlovian behavioral response. Note that Pavlovian autonomic responses were also observed around goal-directed actions (Collet et al., 1997; Amiez et al., 2003). Altogether, these data raise the possibility that LC activation in this and other cognitive tasks is strongly dependent upon the neuronal structures that control the concomitant autonomic activation.

LC and the Truncated Conditioned Reflex

LC neurons fire when the organism faces a behaviorally significant stimulus, either a threat to be avoided, a foe to be fought, or a reward to be obtained, and the activation occurs in parallel with physiological reactions and primitive behavioral reflexes that allow a rapid, stereotyped response to the challenge. An anatomical model to account for the simultaneous activation of LC and the multiple physiological manifestations of the orienting response has been proposed recently, suggesting that LC and the peripheral nervous system are activated by a common input from the NPG (Nieuwenhuis et al., 2010; Pfaff et al., 2012). Thus, LC activation might be considered as part of a general orienting reflex that includes physiological responses such as changes in heart rate, respiration, and pupil dilation, elicited by behaviorally significant stimuli or unexpected changes in the environment.

According to early investigators, electroencephalogram (EEG) desynchronization and pupil dilation always accompany the orienting reflex. In fact, eye movement toward the source of the stimulus, from which the name ''orienting reflex'' is derived, is completely dependent on the level of EEG arousal and degree of dilation of the pupil. When EEG is synchronized and the pupils constricted, there is no eye movement to the stimulus, i.e., no behavioral manifestation of the ''orienting reflex'' (Sokolov, 1963). Thus, it appears that the cortical arousal is related to the behavioral reflex, in this case, eye movement. This strong relation between arousal and behavioral components of the orienting reflex is further supported by a recent experiment in which pupil dilation could be elicited directly by an electrical stimulation of the superior colliculi, which play a critical role in behavioral orienting responses (Wang et al., 2012).

A prime feature of these orienting responses is that they tend to habituate with repetition if the eliciting stimulus is not reinforced. On the other hand, in the presence of reward or punishment, the orienting response is rapidly conditioned. The possibility of conditioning the cortical arousal component of the orienting response was proposed many years ago by Kupalov, a student and close collaborator of Pavlov. Addressing a meeting at the New York Academy of Sciences in 1961, he said, ''… these processes of a general activating character can be reproduced by conditioned reflex means: …. It follows that we may speak of particular conditioned reflexes in which the reaction to the external stimulus culminates not in a definite external reaction, but in a change in the functional state of the brain'' (Kupalov, 1961, p. 1,040). He named this conditioned cortical arousal the ''Truncated Conditioned Reflex'' (TCR) (Kupalov, 1935; cited in Giurgea, 1974). Kupalov went on to suggest that the experimental context acquired the properties of a conditioned stimulus (CS) that could elicit the conditioned response (CR) involving an increase in cortical arousal, attention, and expectancy (Kupalov, 1935, 1948; cited in Giurgea, 1974). Because of the important role of the context in eliciting this response, he called it, alternatively, the ''situational conditioned response'' (Giurgea, 1989). The discovery of the ascending reticular activating system by Moruzzi and Magoun several years later (Moruzzi and Magoun, 1949) provided Kupalov with a brainstem-mediating mechanism for the putative truncated conditioned reflex, lending support to the concept of conditioned regulation of cortical excitation and attention by brainstem afferents (Moruzzi and Magoun, 1949). According to this scheme, the experimental context, for example, the chamber in which the conditioning procedure is carried out, becomes associated with the reinforcement and as such elicits the preparatory reflex. The cortical arousal mediated through the reticular activating system enhances the subsequent explicit CR to the CS (Giurgea, 1974; Sara, 1985). If the ascending reticular activating system mediates the truncated conditioned reflex by arousing the brain and enhancing perceptual and behavioral responses to salient stimuli, this role is shared among the numerous components of the reticular formation. Based on contemporary anatomical literature, the nucleus gigantocellularis is the basis of this system. Cells in the nucleus gigantacellularis respond to sensory stimulation in all modalities and they are considered to be the ''master cells'' for a general arousal function in the brain (Pfaff et al., 2012). These cells have widespread projections to brainstem, pons, midbrain, and basal forebrain. The nucleus gigantacellularis and the neighboring paragiangacellularis are the major excitatory afferent inputs to LC, which, in turn, is in a position to broadcast the message, sending noradrenergic neuromodulatory influences to the entire forebrain. The characteristics of responding LC neurons and their direct relation to autonomic responses as outlined above indict the LC as an intricate, primary, and necessary component of the orienting reflex. An example of an orienting response of an LC neuron can be seen in Figure 2. Single unit recordings of LC were made during differential conditioning of two odors using a go/no go protocol with reward associated with the target odor. The protocol included a preparatory stimulus, a light that preceded the presentation of the odor by 2 s. LC neurons showed a consistent response to the light during the learning session, with no habituation. LC cells stopped responding to the light during extinction; responses to this preparatory stimulus were reinstated as soon as the reward was reinstated in the protocol (from Bouret and Sara, 2004).

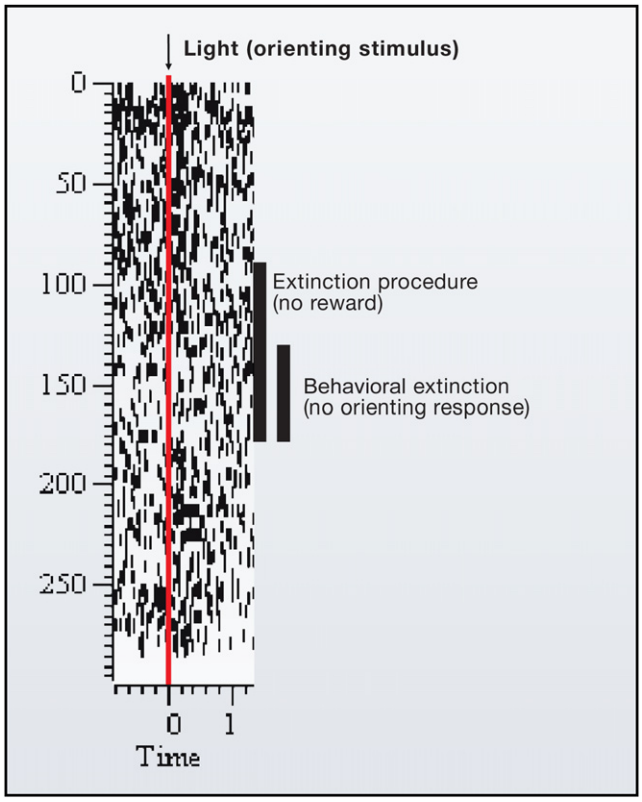

Figure 2. LC Reponse to a Preparatory Stimulus during Differential Conditioning, Extinction, and Reinstatement

Raster display of LC neuronal activity during odor discrimination conditioning trials (for details, see Bouret and Sara, 2004). A brief light stimulus announced the beginning of the trials and the discriminative CS was presented 2 s later. Each dot marks an action potential fired by a single LC neuron recorded while the rat was performing the task. The raster display represents the distribution of action potentials in time, both across trials (on the y axis) and around the light onset within each trial (x axis). Arrow and red line at time 0 represent onset of the light stimulus. Left black bar indicates the beginning of the extinction in which reward was withheld at trial 90. Right black bar represents behavioral expression of extinction, when the rat did not respond to task-relevant stimuli. The reward schedule was resumed at trial 180. Note the phasic response to the light at every trial during the conditioning phase, when the rat readily oriented to the light stimulus indicating trial onset. The response decreased during extinction, with total extinction coinciding with behavioral extinction. Most striking is the reinstatement of the LC response to the light when the CS-reward contingency is reintroduced (relearning) and the animal re-engaged in the task.

In sum, converging evidence indicates that LC neurons are activated by situations that elicit a behavioral orienting response, when the animal interrupts its ongoing activity to face the orienting stimulus. This is in conjunction with autonomic activation mobilizing resources to organize adaptive behavior. Given its widespread influence on forebrain structures, the LC, driven by its major afferent, the NGC, could mediate Kupalov's proposed "Truncated Conditioned Reflex," inducing cortical arousal and resetting network activity in the forebrain.

Locus Coeruleus, Cortical Synchrony, and Arousal

There are both excitatory and inhibitory influences on LC from direct monosynaptic projections from prefrontal cortex (Sara and Hervé-Minvielle, 1995; Jodo et al., 1998). When the two regions are firing in an oscillatory mode, we observed what appeared to be a phasic opposition (Figure 3A) (Sara and Hervé-Minvielle, 1995, Lestienne et al., 1997; Shinba et al., 2000). We recently examined with more precision the phasic relation of LC activity to cortical slow oscillations in nonanesthetized rats and found that about 50% of LC cells were time locked and phase locked to the oscillation, firing about 60 ms after the trough of the down state, during the transition from "down" to "up" state, with no phase overlap between the two populations of neurons (Figure 3B; see also Eschenko et al., 2012). The fact that LC activity is so closely related to spontaneous fluctuations of cortical excitability implies a functional prefrontal-coerulear interaction during slow oscillations. The temporal order of firing of LC and PFC neurons, together with the evidence for LC firing on the ascending edge of the EEG slow wave, suggests that LC may well be involved in promoting or facilitating down-to-up state transitions. While these results do not unequivocally resolve the question of who drives whom, they are compatible with the idea that the LC and the PFC have a mutual excitatory influence. In other words, firing in frontal neurons "wakes up" the LC, and this in turn facilitates the cortical transition to the fully depolarized "up" state.

Time-locked firing of LC neurons in relation to the slow oscillation may have important functional significance for cortical information processing. Sensory-evoked responses in visual cortex vary with spontaneous variations in the levels of network activity, with responses enhanced during the cortical up state of slow oscillations (Haider et al., 2007). This "gain modulation" may be related to the activation of LC neurons just before the fully depolarized cortical state, described above. Released in time with the maximum firing of the cortical neurons, NA would modulate, gate, and tune sensory responses (Berridge and Waterhouse, 2003; Sara, 2009). Active reconfiguration of the functional state of networks may underlie attention, sensory-motor coupling, and other cognitive processes. This is in line with data suggesting that LC firing during the transition from down to up states facilitates the achievement of the maximum depolarized state in the cortex (Eschenko et al., 2012). This mechanism of facilitation of transition to the maximum depolarized state by LC may not be limited to spontaneous oscillations. It may occur each time LC phasic activity is elicited as part of the orienting response or as part of a CR to behaviorally significant stimuli, the equivalent of the cortical TCR.

In the following sections, we will see the extent to which this relation between LC activation, cortical arousal, and the conditioned orienting response to simple environmental challenges extends to cognitive flexibility.

LC Activation during Perceptual Shifts

There is some evidence that pupil dilation varies with spontaneous activity in LC neurons (Aston-Jones and Cohen, 2005), in line with several reports relating the firing of LC neurons with autonomic arousal (Jacobs, 1986; Abercrombie and Jacobs, 1987). Several recent studies have used this noninvasive technique of measuring changes in pupil size in human subjects in an attempt to investigate the role of the LC in cognitive flexibility. A recent example is an experiment aimed at understanding the

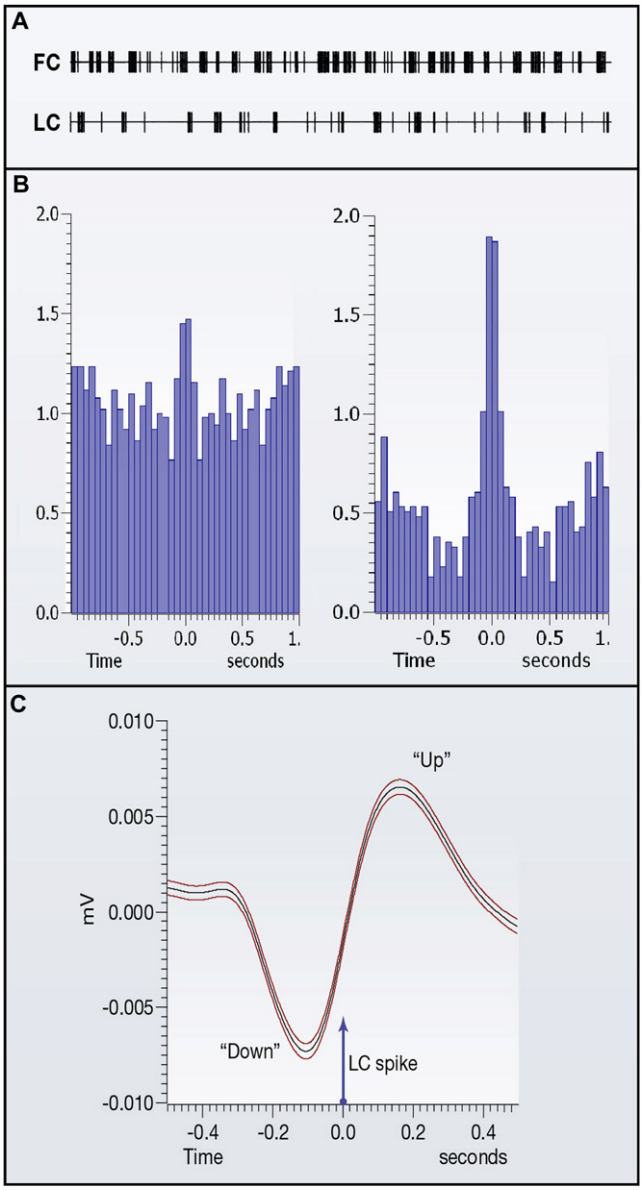

Figure 3. LC Activity in Relation to Behavioral and Cortical Arousal Levels

(A) LC and PFC units fire in phasic opposition. Action potentials from singles units in frontal cortex and LC are recorded simultaneously in the anesthetized rat. When both structures are in an oscillating mode, the firing appears to be in phasic opposition (from Sara and Hervé-Minvielle, 1995). Subsequent studies revealed that LC firing is phase locked to the cortical EEG during sleep-related slow oscillations (Eschenko et al., 2012).

(B) Pattern of LC activity as a function of sleep-wakefulness in nonanesthetized rats. Left: aurocorrelogram of LC multiunit firing during wakefulness. Right: autocorrelogram of firing of the same multiunit population during slow-wave sleep episodes. The firing is synchronous and single units tend to fire in a burst mode.

(C) Spike-triggered average of the EEG. Dark line, mean wave form triggered on LC spikes; shaded area, standard error. Note that the trough, representing the down state, occurs right before LC firing, indicating that LC neurons fire during the transition from down to up state (see Eschenko et al., 2012 for further details).

intrinsic brain mechanisms of bistable perception, a phenomenon in which perception fluctuates between two distinct states when the subject fixates on an ambiguous figure. A typical example is the Necker cube. The state transitions are abrupt and occur spontaneously. The experimental protocol required the subjects to report a state change by pressing a lever. Results showed that pupil dilation occurred just before the change and the amount of dilation predicted the duration of the subsequent perceptual stability (Einhäuser et al., 2008). This experiment does not tell us that LC activation actually caused the abrupt switch in perception, but the loose correlation of the size of the dilation with the duration of the subsequent state suggests a role in maintaining perceptual stability. Using a similar approach, it was established that pupil dilation was reliably associated with uncertainty about the environment and corresponding behavioral adaptation (Jepma and Nieuwenhuis, 2011; Preuschoff et al., 2011; Nassar et al., 2012). A further step toward establishing a causal relation between autonomic arousal and learning was achieved using a simple procedure in which unexpected sounds elicited a transient arousal response, which facilitated learning (Nassar et al., 2012). Given the strong relation between LC activity and arousal, and the fact that LC neurons are phasically driven by unexpected stimuli (Hervé-Minvielle and Sara, 1995; Vankov et al., 1995), these data are all in line with the idea that the LC is involved in promoting behavioral adaptation to unexpected situations (Sara, 1985; Bouret and Sara, 2005; Yu and Dayan, 2005).

LC Activation and the Reorienting System

The LC/NA system has recently been linked to cortical control of attention in a rather fortuitous way by Corbetta et al. (2008). They previously described two separate functional anatomical networks underlying attention: a dorsal frontoparietal network that is responsible for directing attention to expected stimuli and linking them to appropriate responses and a ventral frontoparietal network that detects salient or behaviorally relevant stimuli and interrupts and resets ongoing activity (Corbetta and Shulman, 2002; Shulman et al., 2002). The ventral network is actively suppressed and responds only to behaviorally relevant or unexpected stimuli. When such an event occurs, the ventral network is activated for reorienting, sending a "circuit-breaking" signal to the dorsal region, resulting in a shift of attention to the novel stimulus (Corbetta et al., 2008). There is a striking similarity between this scenario for cortical control of attention and what has been reported concerning activation of the LC neurons by biologically imperative stimuli. Bouret and Sara (2005) proposed that the activation of the LC/NA system induces a "reset" in its target structures, by interrupting existing functional networks and facilitating the emergence of new ones. In that framework, NA would act as a signal from LC, driving the ventral network to "reset" the dorsal region to promote the shift in attention. If LC neurons are coactivated with other elements of an arousal response to behaviorally significant stimuli, NA released in target structures would promote the reorientation of the network, refocusing of attention, and adjustment of behavior. This is strikingly in line with the concept of truncated conditioned reflex proposed by Kupalov.

This hypothesis was recently put to a direct test in an fMRI study in humans (Hermans et al., 2011). Subjects were exposed

to acute aversive stimuli eliciting an abrupt activation of a "salience network" and an increase in connectivity within this network. The salience network was roughly overlapping with the ventral parietal reorienting network described by Corbetta et al. (2008). The increase in strength of the salience network was largely attenuated when subjects were treated with the beta adrenergic receptor antagonist propranolol. The authors conclude that noradrenergic activity "drives a reallocation of neural resources toward a distributed network of regions involved in attention reorienting, vigilant perceptual intake, and autonomic-neuroendrocrine control" (Hermans et al., 2011, p. 1,153).

Truncated Conditioned Reflex, Reorienting, and Memory Retrieval

We borrowed this concept of the TCR to account for the marked facilitation of memory retrieval that can be obtained by a brief exposure to the experimental context before the retention test (Sara, 1985). Rats and humans tend to forget when there is a long interval between the acquisition of information and a recall test. The forgetting is often a "lapse," not a loss, most likely due to a retrieval failure since reminders or psychostimulant drugs, such as amphetamine, can reinstate forgotten memories (Sara and Deweer, 1982; Dekeyne et al., 1986). We found that the most effective reminders to reinstate memory were contextual cues. After a brief exposure to the experimental room right before the retention test, rats showed a maze performance equivalent to that of the last training trial, while control rats placed directly into the maze showed significant forgetting (Deweer et al., 1980). We suggested at the time that the contextual cue, the experimental room, because of its daily association with the food reinforcement during training, becomes a CS, eliciting the TCR of cortical arousal, attention, and expectancy, preparing the rat for efficient maze performance (Sara, 1985). Attempting to understand the biological basis of this robust contextual cue reminder, we stimulated the reticular formation right before the retention test, significantly alleviating the memory deficit (Sara et al., 1980). These experiments were performed before we hypothesized the involvement of the LC in mediating the contextual cue reminder effect, so no attempt was made to pharmacologically block the facilitation by adrenergic receptor blockers. In later experiments, however, using the same behavioral protocol, we found that electrical stimulation of LC likewise alleviated the forgetting and the effect of the stimulation was blocked by pretreatment with the beta adrenergic antagonist propranolol (Sara and Devauges, 1989; Devauges and Sara, 1991). We also showed that pretest treatment with the alpha 2 antagonist idazoxan, at doses that increased firing of LC neurons by about 100%, facilitated retrieval in the same protocol (Sara and Devauges, 1989). The role of the LC/NA system in retrieval from remote memory has since been corroborated by experiments using genetically modified mice and pharmacological manipulation in rats (Murchison et al., 2004).

These studies of contextual cue reminders and arousal were carried out in rodents, but a recent fMRI study confirms that the LC plays a very specific role in retrieval of emotional memories in humans (Sterpenich et al., 2006). Even if the possibility to accurately monitor LC activity using fMRI remains controversial, the location of the activation in this particular study matches that of the LC (Astafiev et al., 2010; Keren et al., 2009). Subjects were presented with neutral faces in emotional or neutral contexts. Their emotional response during the encoding phase was measured by pupil size. Activation of the LC region, as measured by fMRI, was observed during retrieval if, and only if, there had been an emotional response, as indexed by pupil dilation, during the encoding phase. Retention performance was related to the degree of pupil dilation during encoding and LC activation during retrieval (Sterpenich et al., 2006). It is not unreasonable to look upon the LC activation during retrieval as a conditioned response to the learning context, part of the TRC, as suggested by the data from the rat experiments discussed above. Noradrenaline released in the forebrain would have effects in several brain regions that are involved in memory retrieval, including thalamic and cortical regions processing sensory information. Most importantly, it could activate or modulate frontohippocampal networks that are essential for memory retrieval and serve as a reset signal in the ventral parietal network and/or frontal cortex to change the focus of attention (Corbetta and Shulman, 2002; Bouret and Sara, 2005; Corbetta et al., 2008).

Noradrenergic Modulation of Prefrontal Functions

The relatively sparse literature delineating the behavioral contexts driving LC and parallel autonomic responses is complemented by a wealth of experiments showing the essential role played by the LC input to frontal cortex in regulating complex cognitive processes. In an early study, idazoxan, an alpha 2 receptor antagonist that increases firing rate of LC neurons and promotes release of noradrenaline, enhanced the ability of rats to switch between a response strategy and a visual strategy in a complex maze task. There was no effect of the drug on the initial acquisition of the task in either modality; the facilitation was seen only when the rat was required to shift attention from one modality to the other and modify the behavioral strategy (Devauges and Sara, 1991). More recently, Brown and colleagues developed a complex extradimensional shift (EDS) task in which rats had to identify which of the multiple dimensions of a compound stimulus was associated with reward and shift between attentional sets every time the contingency between the stimulus dimension and the reward was changed (Birrell and Brown, 2000). Using this new protocol, several groups have extended the early work on LC/NA involvement on cognitive flexibility, showing that attentional set shifting clearly requires the noradrenergic system, via action in the medial prefrontal cortex (Lapiz and Morilak, 2006; Tait et al., 2007; McGaughy et al., 2008). A particularly convincing recent report from the Valentino laboratory links mild stress acting specifically through the LC with facilitation of attentional set shifting (Snyder et al., 2012). Using the Birrell and Brown set-shifting protocol, they injected different concentrations of CRF into the ventricles (ICV) or directly into the LC region, evaluating the effects on discrimination, intradimensional shift, reversal, and EDS. ICV injections of CRF tended to impair performance on all aspects of the task requiring attention shift. However, when the injections were made directly into the LC region, performance was facilitated on the most difficult stages

of the task, reversal and EDS. Moreover, CRF injections in the LC increased activation of c-*fos* in prefrontal cortex and this activation was correlated with behavioral performance on the EDS. These data thus provide further evidence that activation of LC can facilitate attention shifting by effects on prefrontal cortex.

Electrophysiological data described above indicates that LC activation precedes learning-related changes in frontal activity and before behavioral adaptation. Even more importantly, LC responses to CSs precede responses in frontal regions by tens of milliseconds within the trial. These results contribute to the notion that noradrenaline is especially critical in situations that require a rapid change in attentional focus and behavioral strategy (Bouret and Sara, 2005; Yu and Dayan, 2005; Dayan and Yu, 2006). At first sight, this contrasts with earlier ideas concerning LC/NA role in cognition, which emphasized its implication in sustained attention and working memory (Usher et al., 1999; Aston-Jones and Cohen, 2005; Ramos and Arnsten, 2007; Robbins and Roberts, 2007; Bari et al., 2009). However, both working memory and attentional set shifting rely on the integrity of the prefrontal cortex (Funahashi et al., 1990; Dias et al., 1996, 1997; Goldman-Rakic, 1999; Birrell and Brown, 2000; Fuster, 2008). While there are no experimental data available directly relating LC neuronal activity to working memory, there is a large body of pharmacological data showing the essential role of noradrenergic action in primate prefrontal cortex in executive functions, including behavioral flexibility and attention (Arnsten et al., 2012, this issue of *Neuron*). The release of NA is beneficial, if not necessary, for normal prefrontal cortex function, in particular in complex tasks requiring attention and/or executive control (Arnsten, 2000; Crofts et al., 2001; Robbins and Roberts, 2007; McGaughy et al., 2008; Robbins and Arnsten, 2009). Interestingly, subjects performing complex working memory tasks display an increase in autonomic arousal, measured using skin conductance or pupil dilation (Kahneman and Beatty, 1966; Einhäuser et al., 2010; Howells et al., 2010). The arousal associated with PFC-dependent cognitive processes may reflect a concomitant increase in LC activity, resulting in an increased release of NA necessary for effective performance of the task. Note, however, that the influence of NA on PFC functions is dose dependent and follows an inverted U function. Above a given level, corresponding to high levels of stress, NA becomes deleterious for PFC-dependent executive functions (Arnsten, 2000, 2009). In other words, the positive influence of NA on PFC function would only occur if the arousal-related LC activation is relatively restricted in amplitude and/or in time.

NA Modulation of Synaptic Plasticity

Activation of LC in response to cognitive demands and consequent release of NA in frontal, parietal, and sensory cortices has immediate effects on the focus of attention and selection and processing of the stimuli in the immediate environment. On the other hand, LC also densely innervates limbic structures involved in consolidation of long-term memory (Sara, 2009 for review). There is a large body of evidence that NA plays an essential role in synaptic plasticity in the form of long-term potentiation, underlying long-term memory formation in the hippocampus (Harley, 2007 for review). Noradrenaline in the basolateral amygdala, interacting with opioids and other neuropeptides, is also an important element in memory consolidation (McGaugh and Roozendaal, 2009 for review). A recent study has shown that electrical stimulation of LC can promote long-term potentiation of hippocampal-frontal synapses, which are putatively involved in long-term offline memory consolidation (Lim et al., 2010). There is growing evidence that this involvement of the LC/NA system takes place offline after the initial learning and involves a ''reactivation'' of LC neurons at some time after learning (Tronel et al., 2004; Eschenko and Sara, 2008; Guzmán-Ramos et al., 2012). The mechanism governing this reactivation is currently unknown, but it appears to be independent of the environmental context or cognitive demands. It may be related to ''replay'' of cortical and hippocampal ensembles, activated during learning (Sara, 2010). Replay activity could send excitatory input to LC via the direct projection from frontal cortex. Activation of LC neurons time locked to the ensemble replay would serve to promote long-term synaptic plasticity and memory consolidation. While it is relatively easy to understand how environmental cues of biological significance can trigger firing in LC through the NGC, the nature of the signal re-engaging the LC in the hours after learning remains a mystery (see Sara, 2010 for further discussion).

Conclusion and Perspectives

The key to understanding how behavioral states such as mood, motivation, and arousal can impact cognition in such a dramatic way lies in first understanding the fundamental role LC and other neuromodulators play in regulating cortical activity involved in allocating attention, processing sensory information, and then, offline, regulating synaptic plasticity and memory consolidation. The second key, which has been the focus of the present Review, is to understand the regulation of LC activity.

We have seen that the NA system is mobilized to face environmental challenges, in parallel with the recruitment of autonomic nervous system that responds to homeostatic challenges, environmental stressors, and other impinging stimuli and in turn determines mood and general arousal. In this framework, the autonomic activation would promote the physiological response, whereas the LC would promote an efficient and appropriate cognitive response through its action in the forebrain. Given the rapid LC activation in response to biologically significant events that evoke simple behavioral and autonomic reflexes, it is likely that these phenomena are driven by a common input. In the simplest possible scenario, brainstem nuclei that control autonomic arousal also activate the LC when they are triggered by arousing stimuli (Nieuwenhuis et al., 2010; Pfaff et al., 2012). In that case, LC neurons would simply broadcast the autonomic arousal input to their numerous target regions. But given the direct influence of prefrontal cortices on LC neurons, things are probably not that simple (Sara and Hervé-Minvielle, 1995; Jodo et al., 1998). Top-down influence of prefrontal cortices on both the LC and the autonomic system should modulate their responses in a context-dependent manner. Thus, the implication of the LC in behavioral and cognitive processes probably involves a complex and

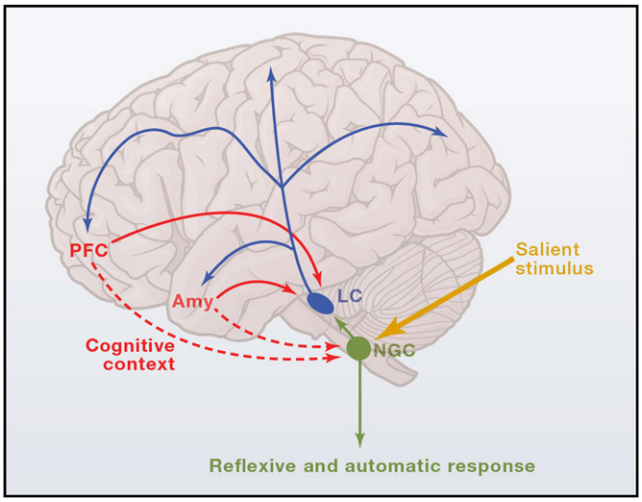

Figure 4. Schematic Overview of the Proposed Mechanisms Underlying LC Activation and Its Function

When a salient or behaviorally significant stimulus occurs (orange arrow), it elicits an activation of LC neurons in parallel with autonomic reflex responses, presumably from a common input, the NGC (green). The intensity of this activation is modulated as a function of the cognitive context, by descending influences from the amygdala and the prefrontal cortex (red). This descending influence could be exerted directly on the LC (full line) or indirectly via the NGC and other brainstem autonomic nuclei (dotted lines). Activation of LC neurons will induce release of noradrenaline in its numerous target regions (blue arrows), including cerebral cortices, limbic structures, thalamus, cerebellum, brainstem, and spinal cord. This surge of NA would facilitate sensory and motor processing and, more generally speaking, the reorganization of distributed functional networks, thereby promoting behavioral adaptation. Activation of LC by the salient context and its functional consequences of facilitation of cortical processing might be considered as an updated version of the "Truncated Conditioned Reflex" proposed by Kupalov at the beginning of the previous century (see text).

dynamic interaction of LC with both subcortical structures controlling autonomic arousal and cortical structures directly involved in attentional and executive functions (Figure 4). Understanding these dynamic interactions is one of the challenges for the future.

Steady advances in electrophysiological recording methods over the years since Kupalov first introduced the concept of conditioned cortical arousal have greatly facilitated the study of the relation between behavioral state, arousal, and cognition. New advances within the last decade should accelerate progress in this direction. fMRI allows us to observe the primate brain performing complex cognitive tasks. Continued refinement of methods now enables visualization of tiny nuclei such as LC, although the temporal resolution is not yet sufficient to capture phasic activation and precise timing of events. On the other hand, rapid development of multichannel, multisite recording and new computing methods give a boost to classical electrophysiological methods for recording from brainstem and cortical ensembles during cognitive activity. Electrophysiological validation of the pupil dilation and other arousal markers as reliable correlates of phasic responses in LC will encourage further research on its role in bistable perception, network reset, and reorienting of attention. These are intriguing hypotheses that await validation. Finally, optogenetics will allow very specific and precise reversible activation and inactivation of the tiny but highly homogeneous noradrenergic nucleus to evaluate impact on cortical activity and cognition (Carter et al., 2010).

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